

**Claims:**

1. A composition comprising bone marrow cells (BMC) and demineralized bone matrix (DBM) or demineralized tooth matrix (DTM), together with a site-responsive polymer, optionally further comprising pharmaceutically acceptable carrier, additive, diluent and/or excipient.
2. A composition according to claim 1, wherein said site-responsive polymer is an RTG polymer.
3. A composition according to claim 2, wherein said RTG polymer is biodegradable.
4. A composition according to claim 1 or 2, wherein said site-responsive polymer is a polymeric system or RTG polymer comprising at least one silicon-containing reactive group.
5. A composition according to claim 4, wherein said site-responsive polymer is biodegradable.
6. A composition according to any one of claims 1 to 5, for use in the transplantation of mesenchymal progenitor cells into any one of a joint, a cranio-facial-maxillary bone, an alveolar bone of maxilla and mandibula, spine, pelvis or long bones of a subject in need.
7. A composition according to any one of claims 1 to 6, for use in the construction or reconstruction of an extraskeletal bone of a subject in need.
8. A composition according to any one of claims 1 to 7, for use for mechanical or biological support of an artificial implant to a joint or of a joint or to a bone of a subject in need.

9. The composition according to any one of claims 1 to 8, further comprising active agents, preferably selected from a bone morphogenetic proteins (BMPs), an immunosuppressant, an immunomodulator, an antibiotic and an anti-inflammatory agents.

10. The composition according to any one of claims 1 to 3 and 6 to 9, wherein said RTG polymer comprises hydrophilic and hydrophobic segments covalently bound by at least one chain extender or coupling agent, having at least two functional groups, wherein the hydrophilic and hydrophobic segments do not display Reverse Thermal Gelation behavior of their own at body temperature and; wherein the viscosity of said polymeric component increases by at least about 2 times upon exposure to a predetermined trigger.

11. The composition according to any one of claims 1 to 3 and 6 to 9, wherein said RTG polymer is a segmented block copolymer comprising polyethylene oxide (PEO) and polypropylene oxide (PPO) chains, wherein said PEO and PPO chains are connected via a chain extender, wherein said chain extender is a bifunctional, trifunctional or multifunctional molecule selected from a group consisting of phosgene, aliphatic or aromatic dicarboxylic acids, their reactive derivatives such as acyl chlorides and anhydrides, diamines, diols, aminoacids, oligopeptides, polypeptides, or cyanuric chloride or any other bifunctional, trifunctional or multifunctional coupling agent, or other molecules, synthetic or of biological origin, able to react with the mono, bi, tri or multifunctional -OH, -SH, -COOH, -NH<sub>2</sub>, -CN or -NCO group terminated hydrophobic and hydrophilic components or any other bifunctional or multifunctional segment, and/or combinations thereof.

12. The composition according to any one of claims 1 to 3 and 6 to 9, wherein said RTG polymer is Pluronic<sup>RTM</sup>, preferably Pluronic F127<sup>RTM</sup> or

F108<sup>RTM</sup>.

13. The composition according to any one of claims 1 to 3 and 6 to 9, wherein said RTG polymer is a random [-PEG6000-O-CO-(CH<sub>2</sub>)<sub>4</sub>-CO-O-PPG3000-]<sub>n</sub> poly(ether-ester) or an alternating [-PEG6000-O-CO-O-PPG3000-]<sub>n</sub> poly(ether-carbonate).
14. The composition according to any one of claims 1 and 4 to 9, wherein said silicon-containing reactive group is capable of undergoing a condensation reaction effected primarily at a predetermined body site in the presence of water and at body temperature wherein said reaction results in an increase in the molecular weight of the polymeric system due to polymerization and/or crosslinking and produces at least a partial change in the rheological and mechanical properties of said system.
15. The composition according to any one of claims 1 and 4 to 9, wherein said responsive polymeric system comprises one or more alkoxy silane groups capable of undergoing a hydrolysis-condensation reaction in the presence of water which reaction is effected primarily at a predetermined body site, said reaction resulting in an increase in the molecular weight of the polymeric system and producing a change in the rheological and mechanical properties of said system.
16. The composition according to any one of claims 1 and 4 to 9, wherein said responsive polymeric system comprises at least one silicon-containing reactive group said at least one group being a mono, di or tri-functional group.
17. The composition according to any one of claims 1 and 4 to 9, wherein said responsive polymeric system generates a polymer selected from the group consisting of a linear polymer, a graft polymer, a comb polymer, a star-like polymer, a crosslinked polymer and combinations thereof.

18. The composition according to any one of claims 1 and 4 to 9, wherein said responsive polymeric system also comprises additional reactive groups selected from the group consisting of hydroxyl, carboxyl, thiol, amine, isocyanate, thioisocyanate and double bond-containing active groups and combinations thereof.

19. The composition according to any one of claims 1 and 4 to 9, wherein said responsive polymeric system also comprises a solid component.

20. The composition according to claim 19, wherein said solid component is a biodegradable material.

21. The composition according to claim 19, wherein said solid component is chemically or physically bound to said responsive polymeric system.

22. The composition according to any one of claims 1 and 4 to 9, wherein said responsive polymeric system is a silicon-containing monomer, oligomer or low molecular weight polymer, being selected from the group consisting of polyoxyalkylene, polyester, polyurethane, polyamide, polycarbonate, acrylic and methacrylic polymers, polyanhydride, polyorthoesters, polyurea, polypeptide, polyalkylene, polysaccharide, and combinations thereof.

23. The composition according to any one of claims 1 and 4 to 9, wherein said responsive polymeric system is selected from a group consisting of a polyoxyalkylene polymer, a block copolymer comprising polyethylene oxide (PEO) and polypropylene oxide (PPO) selected from the group consisting of a diblock, a triblock or a multiblock, a segmented block copolymer comprising polyethylene oxide (PEO) and polypropylene oxide (PPO) chains, wherein said PEO and PPO chains are connected *via* a chain extender, a poly(alkyl-co-oxyalkylene) copolymer having the formula  $R-(OCH_2CH)_n-OH$ , where R is an

hydrophobic monofunctional segment selected from a group consisting of poly(tetramethylene glycol), poly(caprolactone), poly(lactic acid), poly(siloxane) and combinations thereof, a poly(alkyl-co-oxyalkylene) copolymer having the formula  $[-R'-(OCH_2CH)_n-O]_pH$ , where  $R'$  is a bifunctional or multifunctional hydrophobic segment, a poly(N-alkyl substituted acrylamide), preferably poly(N-isopropyl acrylamide), cellulose and cellulose derivatives and combinations thereof.

24. The composition according to any one of claims 1 and 4 to 9, wherein said responsive polymeric system is a segmented block copolymer comprising polyethylene oxide (PEO) and polypropylene oxide (PPO) chains, wherein said PEO and PPO chains are connected *via* a chain extender, wherein said chain extender is selected from a group consisting of phosgene, aliphatic or aromatic dicarboxylic acids or their reactive derivatives such as acyl chlorides and anhydrides or other molecules able to react with the OH terminal groups of the PEO and PPO chains, such as dicyclohexylcarbodiimide (DCC), aliphatic or aromatic diisocyanates selected from a group consisting of hexamethylene diisocyanate (HDI) or methylene bisphenyldiisocyanate (MDI) or cyanuric chloride or any other bifunctional or multifunctional segment and combinations thereof.

25. The composition according to claim 23, wherein said poly(N-alkyl substituted acrylamide) is a copolymer comprising alkoxysilane-containing vinyl monomers.

26. The composition according to any one of claims 1 and 4 to 9, wherein said responsive polymeric system is selected from a group consisting of alginates and its derivatives, hyaluronic acid and its derivatives, collagen, gelatin, chitosan and its derivatives, agarose, cellulose and its derivatives, water soluble synthetic, semi-synthetic or natural oligomers and polymers selected from a groups consisting of oligoHEMA, polyacrylic acid, polyvinyl

alcohol, glycerol, polyethylene oxide, TMPO, oligo and polysaccharides, oligopeptides, peptides, proteins, enzymes, growth factors, hormones, drugs and combinations thereof.

27. The composition according to any one of claims 6 to 26, wherein said subject is a mammal, preferably a human.

28. The composition according to any one of claims 1 to 27, wherein the DBM is of vertebrate origin.

29. The composition according to claim 28, wherein the DBM is of human origin.

30. The composition according to any one of claims 1 to 29, wherein the DBM is in powder, particles, string or sliced form.

31. The composition according to claim 30, wherein said DBM is in powder or particle form, wherein the particle size of the DBM is about 50 to 2500 $\mu$ , preferably about 250 to 500 $\mu$ .

32. The composition according to any one of the claims 1 to 31, wherein the ratio between BMC and DBM is between 1:1 and 20:1 (volume:volume), preferably between 2:1 and 9:1 (volume:volume), particularly 4:1 (volume:volume).

33. The composition according to any one of claims 1 to 32, wherein said composition contains BMC-DBM mixture and RTG polymer at a ratio between 5:1 to 1:5, preferably between 3:1 and 1:2, particularly at a ratio of 2 parts BMC-DBM mixture to 1 part of RTG polymer material in fluid form (volume:volume).

34. The composition according to any one of claims 1 to 33, for restoring and/or enhancing the formation of a new hyaline cartilage and/or subchondral bone structure.

35. The composition according to any one of the preceding claims, for the treatment of a patient suffering from any one of hereditary or acquired bone disorder, hereditary or acquired cartilage disorder, a primary malignant bone or cartilage disorder, bone defects due to metastases or bone lesions due to a hematopoietic malignancy, particularly multiple myeloma, metabolic bone diseases, bone infections, conditions involving congenital or acquired bone or cartilage deformities and Paget's disease.

36. The composition according to any one of claims 1 to 37, for the treatment of a patient in need of any one of correction of complex fractures, bone replacement and formation of new bone in plastic or sexual surgery.

37. The composition according to any one of claims 33 to 36, wherein the number of bone marrow cells in the composition is from about  $10^6$  to  $4 \times 10^{10}$  cells/ml.

38. A method for transplantation of a mixture comprising BMC with DBM, together with a site-responsive polymer, and optionally further comprising pharmaceutically acceptable carrier or diluent and/or additional active agent/s, into any one of a joint, a cranio-facial-maxillary bone, an alveolar bone of maxilla and mandibula, spine, pelvis and a long bone, or for construction or reconstruction of an extraskeletal bone, including for mechanical or biological support of artificial implants to a joint or of a joint or to a bone of a subject in need, wherein said method comprises introducing into said joint or bone a composition as defined in any one of claims 1 to 37.

39. The method according to claim 38, wherein said mixture is administered non-invasively by a syringe, an arthroscopic procedure or by open surgery into the site of implantation.

40. A method of treating a damaged joint, post traumatic, inflammatory, autoimmune, infectious or degenerative etiology associated with malformation and/or dysfunction of cartilage and/or subchondral bone in a mammal, preferably a human in need of such treatment, comprising administering into an affected joint or bone of said mammal a composition according to any one of claims 1 to 37.

41. The method according to claim 40, wherein the BMC comprised in said composition are either allogeneic or said mammal's own.

42. A non-invasive implantation method for support of implants of joints or other musculoskeletal implants, comprising introducing a graft into a joint or a cranio-facial-maxillary bone of a subject in need, wherein said graft comprises a composition according to any one of claims 1 to 37.

43. Use of a composition according to any one of claims 1 to 37, as a graft of mesenchymal and/or mesenchymal progenitor cells for transplantation/implantation into a mammal, preferably a human.

44. The use according to claim 43, wherein the transplantation is into a joint or into a cranio-facial-maxillary bone of said mammal.

45. The use according to any one of claims 43 or 44, wherein said transplantation is for the development of new bone and/or cartilage.

46. The composition according to any one of claims 1 to 37, for use in the treatment of a patient suffering from any one of a hereditary or acquired bone



disorder, a hereditary or acquired cartilage disorder, a primary or secondary malignant bone or cartilage disorder, metabolic bone diseases, bone infections, conditions involving bone or cartilage deformities due to traumatic, infectious, inflammatory, autoimmune etiology and Paget's disease.

47. The composition according to any one of claims 1 to 37, for use in the treatment of a patient in need of any one of correction of complex fractures, bone replacement and formation of new bone in plastic and sexual surgery.

48. Use of a mixture of BMC with DBM, together with a site-responsive polymer, in the preparation of a graft for the treatment of a bone or cartilage disorder.

49. A kit for performing transplantation of BMC in admixture with DBM and a site-responsive polymer into any one of a joint, a cranio-facial-maxillary bone, an alveolar bone of maxilla and mandibula, spine, pelvis and long bones, or for construction or reconstruction of an extraskeletal bone, including for mechanical or biological support of artificial implants to the joint or of the joint or to the bone of a mammal, wherein said kit comprises:

- (a) DBM in powder, particle, string or slice form;
- (b) a site-responsive polymer;
- (c) a BM aspiration needle;
- (d) an intra-osseous bone drilling burr;
- (e) a needle with a thick lumen for infusion of viscous bone marrow-DBM-site-responsive polymer mixture;
- (f) a 2-way lumen connector for simultaneous mixing of BMC with DBM and site-responsive polymer and diluent;
- (g) a medium for maintaining BMC; and optionally
- (h) additional factors stimulating osteogenesis; and
- (i) cryogenic means for handling and maintaining BMC or BMC together with DBM.

50. The kit according to claim 49, optionally further comprising a carrier and/or diluent for the BMC and DBM mixture, and for the site-responsive polymer.